Epitomes

Important Advances in Clinical Medicine

Psychiatry

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under its direction.

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Advances in the Treatment of Alcoholism

A PUBLISHED DEFINITION OF alcoholism has been useful in both clinical practice and medical education. Alcoholism is described as a chronic primary disease. This research-based concept is useful in supporting abstinence-based treatment that links patients with alcoholism into the 12-step program of Alcoholics Anonymous. This new definition also supports the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised, describing loss of control over the use of alcohol and a continued use despite adverse consequences.

Abstinence from alcohol and other addicting drugs is now well accepted as a first goal in the treatment of alcoholism. Anxiety and depression, so commonly associated with alcoholism, usually clear with abstinence and continued treatment. A consensus has developed that, unless the emotional problems are severe enough to interfere with patients' ability to participate in treatment, chemotherapy—antidepressants—should not be started until two to eight weeks after detoxification has been completed.

The problems of a dual diagnosis of psychiatric disorders and alcoholism have become increasingly well recognized in treatment settings. These complex problems require combined treatment. In most clinical settings, this is best done concurrently, with the alcoholism and psychiatric treatment teams cooperating with one another. Criteria are still being developed for matching patients with a dual diagnosis with the most effective treatment.

A structured treatment of alcoholism, which emphasizes education, group therapy, family involvement, and an intense introduction to Alcoholics Anonymous, has recently received research attention. A controlled study of alcoholic employees found that those who entered Minnesota model abstinence-based inpatient treatment were significantly more likely to be abstinent and active in Alcoholics Anonymous than those who were only sent to Alcoholics Anonymous or who could choose their treatment. Costs were similar for each group.

Research continues to confirm the importance of Alcoholics Anonymous in achieving stable sobriety. Both prospective and retrospective studies have shown that going to the meetings is a significant ($P < .001$) predictor of sobriety; having a sponsor and using a phone list both significantly ($P < .05$) reduced the risk of relapse; and 91% of people with alcoholism who become sponsors are in stable sobriety at ten-year follow-ups.

Physicians, and especially psychiatrists, are in an excellent position to help these patients overcome their resistance to Alcoholics Anonymous. A program of recovery in Alcoholics Anonymous complements medical and psychiatric treatment and promotes normal growth and development.

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Clozapine Update

CLOZAPINE is a unique antipsychotic medication that is especially effective in patients suffering from treatment-resistant schizophrenia. Although clozapine was developed more than 30 years ago, its use was restricted in the United States because of the occurrence of agranulocytosis in 1% to 2% of patients after its release in Europe.

Current literature suggests that clozapine is also effective in patients with schizoaffective disorder, and studies are being done to test its efficacy in a variety of psychiatric disorders. Delusions, hallucinations, disordered

thought, and aggressive behaviors may all be dramatically alleviated when compared with the response to standard antipsychotic treatments. In patients with symptoms such as withdrawal and apathy, the response to clozapine may be particularly dramatic. Patients with chronic schizophrenia who take clozapine appear to have substantially improved quality of life compared with patients on standard neuroleptic treatments. Anecdotal reports suggest that clozapine may have special efficacy for patients with severe schizophrenia early in their illness. Clozapine doses range from 25 to 900 mg per day.

Clozapine is largely free of the extrapyramidal side effects that are so common with ordinary antipsychotics. Tardive dyskinesia (late, persistent, orofacial dyskinesia) from clozapine use is rare, and clozapine treatment has substantially lessened the symptoms of tardive dyskinesia in many patients.

Clozapine's neurochemical profile is complex. A basis for its unique action may be a particular pattern of preference for D_2-dopamine receptors over D_1 receptors. Clozapine also has a complex relationship with serotonin, γ-aminobutyric acid, muscarinic, and other systems in the brain.

The manufacturer requires that a patient's weekly leukocyte count be above an "agranulocytosis threshold" of 2×10^9 per liter (2,000 per μl) before each week's supply of medication is released. Monitoring the granulocyte count to a threshold of 1 granulocyte $\times 10^9$ per liter (1,000 per μl) may be a more sensitive indicator. Half of reported episodes of agranulocytosis occur within three months of starting treatment, but weekly monitoring of leukocyte counts continues indefinitely. When agranulocytosis occurs, 14 days of isolation from exogenous infectious agents are usually necessary until the granulocyte count recovers. Treatment with filgrastim (granulocyte colony-stimulating factor) reduces the average duration of clozapine-induced agranulocytosis to about seven days.

Other side effects seen with clozapine use include fever, seizures, constipation, tachycardia, sedation, and sialorrhea. About 5% of patients will have a seizure at doses of more than 600 mg per day. These patients can usually be treated with a dosage reduction and divalproex sodium maintenance. Tachycardia and fever are both common when clozapine treatment is started. Rapidly raising the dose above 300 mg, using the necessary titration schedule, seems to be the best way to manage fever. Severe constipation can occur and can require aggressive bowel management. A dose-dependent sialorrhea is a puzzling side effect in a medication that otherwise has strong anticholinergic properties.

Despite its side effects and the required intensive monitoring, clozapine remains a uniquely effective medication in the management of treatment-resistant schizophrenia.

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Dementia Complex of the Acquired Immunodeficiency Syndrome

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) dementia complex, also known as human immunodeficiency virus (HIV-1)-associated dementia complex, is the most common central nervous system complication of HIV infection. It is characterized by deficiencies in cognition-motor performance and sometimes behavioral changes. Although the natural history and severity of this complex can vary and the actual incidence is debated, AIDS dementia complex causes serious morbidity and mortality in a considerable number of people with AIDS.

The AIDS dementia complex is a severe form of HIV-1-associated cognitive-motor complex that includes a broad spectrum of clinical manifestations and severity. Early symptoms can be subtle and apparent only with neuropsychological testing. Severe symptoms include global cognitive and motor dysfunction with florid dementia and death. Key cognitive symptoms of this complex include memory loss, decreased concentration, decreased attention span, and visuospatial disorientation. Patients often have behavioral changes such as apathy, loss of interest in usual activities, social isolation (withdrawal), or irritability. Because AIDS dementia complex is a subcortical dementia, early motor deficits are common. In particular, generalized slowing, ataxia, tremors, incoordination, lower extremity weakness, spasticity, and hyperreflexia can develop. This is different from Alzheimer's disease and other cortical dementias that present with more obvious intellectual deterioration. The deficits of AIDS dementia complex are like a record that is being played too slowly; those of Alzheimer's disease, in contrast, are more like a record that skips.

Clearly the symptoms of AIDS dementia complex overlap with those of other affective psychiatric and neurological disorders. For example, depression, drug intoxication, delirium, neurosyphilis, cryptococcal meningitis, toxoplasmosis, lymphoma, and progressive multifocal leukoencephalopathy are all important in the differential diagnosis of patients with mental status changes. A thorough workup is imperative to rule out these disorders that require different treatment methods. Evaluation should include a cranial imaging study (preferably a magnetic resonance imaging scan, which is more sensitive than computed tomography) with contrast enhancement and a lumbar puncture for cerebrospinal fluid studies. Neuropsychological testing can provide a quantitative serial assessment with early AIDS dementia complex, but it is usually not a major tool in diagnosis.

Although this complex is not considered curable, interventions can stabilize or reverse symptoms and improve living function, even with advanced symptoms. For cognitive impairment, high-dose zidovudine (1 to 2 grams orally per day) continues to be the most effective treatment. Other antiretrovirals, with the possible exception of stavudine (d4T), do not readily cross the blood-brain barrier. Human immunodeficiency virus type 1 is thought to cause neuronal death not by direct viral infection, but indirectly by generating toxic products such as HIV gp120 and cellular cytokines (interleukins, tumor necrosis fac-